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Risk Factors for Severe Hyperbilirubinemia among Infants with Borderline Bilirubin Levels: A Nested Case-Control Study

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Abstract

Objective—To estimate the effect of phototherapy and other predictors on the risk of total serum bilirubin (TSB) ≥ 25 mg/dL in infants with a TSB of 17 to 22.9 mg/dL at age ≥ 48 hours.

Study design—From a cohort of 285295 infants ≥ 34 weeks gestation and ≥ 2000 g born between 1995 and 2004 in northern California Kaiser hospitals, we identified 17 986 with a TSB of 17 to 22.9 mg/dL at age ≥ 48 hours. All infants exhibiting a TSB ≥ 25 mg/dL were selected as cases for the study. Four randomly selected controls were matched to each case based on the difference between their qualifying TSB and the American Academy of Pediatrics' phototherapy threshold.

Results—A total of 62 cases were identified (0.4%). Six of these (10%) received inpatient phototherapy within 8 hours, along with 101 controls (41%) (adjusted odds ratio [AOR] 0.15; 95% confidence interval [CI] 0.06 to 0.40). Cases more often had lower gestational age (AOR 3.24; 95% CI 1.24 to 8.47 for 38 to 39 weeks and AOR = 3.70; 95% CI 0.61 to 22.4 for 34 to 37 weeks compared with ≥ 40 -week infants), bruising, (AOR 2.52; 95% CI 1.16 to 5.50), exclusive breast-feeding (AOR 2.09; 95% CI 1.05 to 4.03), and TSB increase of ≥ 6 mg/dL/day (AOR 2.39; 95% CI 1.18 to 4.85).

Conclusions—Phototherapy was 85% effective in preventing TSB ≥ 25 mg/dL. The strongest predictors of TSB ≥ 25 mg/dL were gestational age, bruising, family history, and rapid rise in TSB.

Clinicians caring for newborns often must decide how to manage those presenting with jaundice in the first few days after birth. If the infant's total serum bilirubin level (TSB) is well above or below the American Academy of Pediatrics (AAP) jaundice treatment guidelines (based on age [in hours] and TSB level),¹ then management decisions are simple. But marked variability exists in the treatment of infants with TSB levels within a few mg/dL of the AAP's age-specific phototherapy threshold.² A physician may choose to admit the infant for inpatient phototherapy, implement interventions at home (home phototherapy, supplementation with formula), or follow the TSB level with serial measurements. Because TSB levels in this range often peak below 25 mg/dL without receiving treatment, it may be reasonable to observe an infant and repeat the test. In addition, even though many consider inpatient phototherapy a benign intervention, it does have some drawbacks, including

additional expense,³ interruption of breast-feeding,^{4,5} conveyance of a sense of vulnerability in the child,^{4,6,7} and disruption of maternal–infant bonding. On the other hand, failure to initiate phototherapy could lead to an infant developing bilirubin levels possibly necessitating exchange transfusion.

In an infant with a TSB level near the AAP threshold for phototherapy, what factors besides bilirubin level and the infant's age should help guide management decisions? Variability in practice suggests that physicians are not following the AAP guidelines strictly. This variability may be due to the guideline's lack of precision, possibly reflecting their development by expert opinion rather than by epidemiologic research to define risk thresholds.

Earlier studies focusing on measurements made during the birth hospitalization have found correlations between family history of jaundice, exclusive breast-feeding, bruising, cephalohematoma, lower gestational age, and Asian race and increased risk of hyperbilirubinemia.^{8–11} Whether these same risk factors predict a TSB ≥ 25 mg/dL in the subset of patients who are already near the AAP's threshold for phototherapy is unknown, but nonetheless they are relevant for phototherapy treatment decisions in these borderline cases.

Despite its frequent use, few controlled trials of phototherapy exist. Studies initiating phototherapy at 13 to 19 mg/dL to prevent a TSB ≥ 20 mg/dL have shown a relative risk reduction of 30% to 60% and an absolute risk reduction of 5% to 10%, corresponding to a number of patients needed to treat of 10 to 20.^{12–14} No studies have addressed the efficacy of phototherapy at higher bilirubin levels than those currently recommended, for example, beginning at TSB levels of 17 to 22.9 mg/dL with a goal of maintaining TSB < 25 mg/dL. In addition, the phototherapy used in existing studies was less intensive (ie, lower irradiance) than that used today.

The objectives of the present study were to determine the frequency and predictors of TSB ≥ 25 mg/dL and to assess the efficacy of phototherapy and other interventions in infants presenting with TSB between 17 and 22.9 mg/dL at 48 hours or longer after birth.

Methods

Study Design

This nested case-control study began with a cohort of 285 295 infants born in northern California Kaiser Permanente Medical Care Program (KPMCP) hospitals between January 1, 1995 and December 30, 2004, who were at least 34 weeks gestational age and weighed ≥ 2000 g at birth. The KPMCP has information systems built around a common medical record number, permitting linkage across multiple laboratory and neonatal databases.^{2,15–17}

Subjects

The Figure illustrates the sample selection. We identified 17 986 infants with a TSB level between 17 and 22.9 mg/dL at 48 hours or more after birth. An infant's first TSB in this range was defined as the qualifying TSB. We excluded any infants with (1) a first TSB level between 17 and 22.9 mg/dL after a TSB of ≥ 23 mg/dL (ie, jaundice already appeared to be resolving), (2) the maximum TSB level that was also the last TSB level (ie, a subsequent decline in TSB was not documented), or (3) a conjugated (or direct) bilirubin level ≥ 2 mg/dL at the time of the qualifying TSB level. These criteria excluded 4 143 infants, leaving a cohort of 13 843. During the study period, the KPMCP had no program-wide protocols for neonatal jaundice management; individual facilities determined these until 2005, when a

program-wide guideline was implemented. Beginning in 1997, follow-up within 48 hours of discharge was arranged for all infants born at KPMCP hospitals in northern California.

We defined the cases as those infants with a maximum TSB ≥ 25 mg/dL after the qualifying TSB. We matched 4 control infants to each case. Infants were first matched on their risk group as defined by the 2004 AAP hyperbilirubinemia treatment guidelines. These guidelines summarize phototherapy recommendations in a graph with 3 curves that indicate the threshold TSB level for phototherapy given the infant's age, gestational age, and the presence of additional risk factors (eg, a positive direct antiglobulin test [DAT] or signs of illness).¹ Because we knew the gestational age and DAT results, we classified infants as follows, incorporating both time and bilirubin level: low risk, ≥ 38 weeks gestation and negative DAT; medium risk, ≥ 38 weeks gestation and positive DAT or < 38 weeks gestation and negative DAT; high risk, < 38 weeks gestation and positive DAT. Next, we matched infants on the difference (in mg/dL) between their qualifying TSB level and the AAP threshold for phototherapy for their risk group.

Predictor Variables

We abstracted data from electronic and paper records of admissions, outpatient visits, and home health visits until the time at which TSB reached 25 mg/dL or reached its maximum and a decline was documented. To measure fractionated bilirubin, 11 of the 12 participating hospitals used the Ektachem system and reported conjugated bilirubin measurements; the remaining hospital used the diazo method and reported direct bilirubin measurements. We collected information on feeding (breast-feeding vs formula feeding), and other risk factors for hyperbilirubinemia (e.g., bruising, cephalohematoma, breast-feeding problems, weight loss, and family history of jaundice). For these variables, we considered only values recorded in the medical record within 8 hours of measurement of the qualifying TSB level to avoid any biased ascertainment that might occur after a future rise in TSB. Interventions abstracted included instructions to expose the infant to sunlight, home and inpatient phototherapy, exchange transfusion, intravenous immunoglobulin (IVIG), and phenobarbital. Various phototherapy devices were used at KPMCP during the study; the most frequently used devices were manufactured by Hill-Rom Airshields Inc, Hatboro, Pennsylvania (41%), Olympic Medical Corporation, Seattle, Washington (27%), and Datrex Ohmeda, Louisville, Colorado (24%). Data on the specific model used for each infant are not available, however.

We obtained bilirubin levels, results of direct antiglobulin testing, and basic demographic data (birth weight, gestational age, race) from KPMCP databases. To estimate the efficacy of phototherapy, we included inpatient phototherapy started within 8 hours of a qualifying TSB level and home phototherapy started within 1 day of the qualifying TSB level. The exact time of initiation of home phototherapy was not available in most cases; however, we were able to determine the day of initiation from notes in the medical record and the delivery date for the home phototherapy unit in the durable medical equipment database.

We calculated the rate of rise in TSB as the qualifying TSB minus the preceding TSB divided by the change in time (hours). If the infant's qualifying TSB was the first TSB, then we assumed that the infant had a TSB of 1.5 mg/dL at birth. We dichotomized the rate of rise at the median value (6 mg/dL/day or 0.25 mg/dL/hour). Any infant with no documented formula feeding or formula supplementation after the qualifying TSB, up to when the TSB either declined or reached ≥ 25 mg/dL, was considered to have been exclusively breast-fed after the qualifying TSB.

Statistical Methods

We compared differences between baseline characteristics of cases and controls using repeated-measures analysis of variance (for continuous variables) and conditional logistic regression (for binary variables), to account for the matched sampling. We derived likelihood ratio–based confidence intervals for variables with a 0% rate among the cases (ie, exchange transfusion, use of intravenous immunoglobulin [IVIG], and use of intravenous fluids after qualifying TSB). To test the efficacy of inpatient phototherapy and evaluate risk factors, we performed conditional logistic regression with case status (TSB $\geq$ 25 mg/dL) as the dependent variable and the factor of interest as the independent variable. Finally, based on previous studies, we developed a multivariate conditional logistic regression model with TSB $\geq$ 25 mg/dL as the outcome and the independent variables race, sex, gestational age, physical examination findings, family history, phototherapy within 8 hours, and formula supplementation. We dropped variables from the final model if they were poor predictors ($P > .1$). We calculated adjusted odds ratios (AORs) for each predictor in the final model, and evaluated the discrimination of the final model using the c -statistic.¹⁸ We performed all analyses using Stata 9.0 statistical software (StataCorp, College Station, TX).

This study was approved by the KPMCP Institutional Review Board, which has jurisdiction over all medical centers and clinics included in this study, and also by the Committee on Human Research at the University of California San Francisco.

Results

There were 17,986 infants with a TSB between 17 and 22.9 mg/dL at age $\geq$ 48 hours. Of this group, 62 infants reached a TSB $\geq$ 25 mg/dL. For 1859 infants, their last TSB was also their highest TSB measured, suggesting incomplete follow-up. The maximum TSB levels of these 1859 infants were drawn at a mean age of 4.5 days, and 92% were $<$ 20 mg/dL.

Table I summarizes characteristics of the study cohort. The cases and controls did not differ significantly by sex, race, birth weight, or duration of birth hospitalization. The 2 groups had similar qualifying TSB levels (mean $\pm$ standard deviation: cases, 20.2 ± 1.6 mg/dL; controls, 20.1 ± 1.6 mg/dL) and percentage of weight loss from birth (cases, $6.3\% \pm 3.7\%$; controls, $6.0\% \pm 3.5\%$). The matching variables were distributed identically in the cases and controls, with 3% of the infants meeting the AAP's criteria for high risk 39% for intermediate risk, and 58% for low risk. Each group's qualifying TSB levels averaged 3.6 mg/dL above the AAP's phototherapy threshold for age and risk group. Six cases (10%) and 101 controls (41%) received inpatient phototherapy within 8 hours of their qualifying TSB. Of the infants who underwent phototherapy, 59 (55%) had triple phototherapy, 45 (42%) had double phototherapy, and 2 (2%) had single phototherapy. In 1 infant, the number of phototherapy lights used could not be discerned from the chart.

Table II shows the results of our bivariate analysis. Infants born at lower gestational age and those with a birth hospitalization $<$ 48 hours tended to be at higher risk for developing severe hyperbilirubinemia. Sex and race were not predictive individually or when coupled (eg, male Asian). History and physical examination findings did not predict severe hyperbilirubinemia, except for bruising on examination. Weight loss $\geq$ 10% and type of feeding before qualifying TSB level were not predictive. Infants who had a qualifying TSB after being discharged from the birth hospitalization or who had a TSB increase of $\geq$ 6 mg/dL/day were found to be at an increased risk of developing severe hyperbilirubinemia. DAT results demonstrated no association with the risk of severe hyperbilirubinemia.

Inpatient phototherapy was highly protective, with an odds ratio (OR) of 0.14 (95% confidence interval [CI] = 0.06 to 0.34; $P < .001$). Home phototherapy was not significantly

effective; however, only 11 infants in the study received it. None of the infants who received IVIG ($n = 5$), exchange transfusion ($n = 2$), or intravenous fluids ($n = 22$) developed severe hyperbilirubinemia. Infants who were exclusively breast-fed after the qualifying TSB had twice the risk of developing $TSB \geq 25$ mg/dL.

We also examined whether the efficacy of phototherapy differed in infants with a positive DAT compared with those with a negative or missing DAT. No infants with a positive DAT who received inpatient phototherapy exhibited a $TSB \geq 25$ mg/dL. In 15% of the infants, the physician recommended placing the infant in sunlight; however, this intervention did not appear to reduce the risk of severe hyperbilirubinemia ($OR = 1.30$; 95% $CI = 0.63$ to 2.72).

Table III displays the results of our final multivariate model. The model demonstrated good discrimination, with a c -statistic of 0.82 (95% $CI = 0.76$ to 0.88). Lower gestational age increased an infant's risk of reaching a $TSB \geq 25$ mg/dL. Compared with infants of ≥ 40 weeks gestation, infants born at 38 to 39 weeks gestation had an AOR of 3.12 (95% $CI = 1.21$ to 8.03). Although not statistically significant, a similar trend was seen in infants of 34 to 37 weeks gestation, who exhibited an AOR of 3.74 (0.62 to 22.7). A family history of jaundice appeared to increase the risk of severe hyperbilirubinemia by almost 4-fold (AOR = 3.83; 95% $CI = 0.93$ to 15.7), and bruising on examination doubled this risk (AOR = 2.36; 95% $CI = 1.17$ to 4.77 .) Infants with a TSB increase of ≥ 6 mg/dL/day had an AOR of 2.54 (95% $CI = 1.17$ to 5.50). Inpatient phototherapy remained strongly protective (AOR = 0.15; 95% $CI = 0.06$ to 0.40). Those infants who exclusively breast-fed after their qualifying TSB had an AOR of 2.03 (95% $CI = 1.03$ to 3.99).

Discussion

Our study illustrates what factors physicians should take into account when making difficult treatment decisions in infants with TSB between 17 and 22.9 mg/dL at 48 hours or longer after birth. At study entry, 97% of the infants had a TSB level above the 2004 AAP threshold for phototherapy; however, only 35% of all infants received inpatient phototherapy. This underscores the substantial variation in treating these infants and the need for an evidence-based approach to treating neonatal hyperbilirubinemia.

Despite matching cases and controls based on AAP risk group (which includes 2 gestational age categories), gestational age was an important predictor of a $TSB \geq 25$ mg/dL. Our findings support the 2004 AAP guidelines that recommend initiating phototherapy at lower TSB levels in late preterm infants.¹ These infants may require closer follow-up than term infants to identify elevated TSB levels to enable prompt initiation of treatment.

Unlike previous studies that found Asian race and male sex to be risk factors for jaundice and African-American race to be protective, we found that once the TSB reached 17 to 22.9 mg/dL, race and sex were no longer important predictors of which infants would develop a $TSB \geq 25$ mg/dL. Of the other history and physical examination findings, only family history of jaundice and bruising remained in the model. The fact that family history appeared to be a risk factor, placing infants at almost 4-fold greater risk for severe hyperbilirubinemia, suggests the possible importance of genetic contributions in determining the genesis of neonatal hyperbilirubinemia. Polymorphisms in the genes encoding for the hepatic bilirubin-conjugating enzyme uridine diphosphate glucuronosyltransferase 1A1 or other enzymes involved in bilirubin metabolism may be important in predicting who will develop severe hyperbilirubinemia and merit further investigation.¹⁹⁻²¹ Why cephalohematoma is not a risk factor and bruising is a risk factor is unclear; it may be a chance finding (because the confidence intervals for bruising and cephalohematoma overlap), or there may have been measurement error in identifying cephalohematoma. Our

finding that infants with > 10% weight loss from birth were not at higher risk for TSB $\geq$ 25 mg/dL may be because the weight loss led to interventions to improve nutrition and hydration.

Although infants with hyperbilirubinemia often have some degree of breast milk or breast-feeding jaundice, we found that the type of feeding just before developing a TSB in the qualifying range was not predictive of reaching a TSB $\geq$ 25 mg/dL. On the other hand, infants who received formula supplements or received only formula after the qualifying TSB were half as likely to reach a TSB $\geq$ 25 mg/dL compared with infants who breast-fed exclusively. This finding is consistent with the average 50% reduction in relative risk found in a randomized trial conducted by Martinez et al,¹⁴ in which the decline in TSB level was significantly larger when phototherapy was combined with formula. Formula supplementation may be considered in newborns approaching threshold bilirubin levels for phototherapy, because it may help prevent the need for phototherapy and hospitalization. Although formula feeding sometimes may interfere with breast-feeding, it may have less affect than admitting an infant to the hospital for phototherapy.

Laboratory tests can be helpful in predicting which infants will develop severe hyperbilirubinemia (TSB $\geq$ 25 mg/dL). A TSB increase of $\geq$ 6 mg/dL/day doubled the risk of developing severe hyperbilirubinemia. We could not address the effect of the qualifying TSB level itself, because this was used for matching the cases and controls. In our preliminary analyses, we found that the amount either above or below the AAP phototherapy guidelines was the most important predictor of reaching a TSB 25 mg/dL. We matched on this variable in these analyses to better identify other predictors. A positive DAT was not associated with an increased risk of severe hyperbilirubinemia in this cohort. Moreover, we found no evidence of decreased effectiveness of phototherapy in those with a positive DAT; in fact, there were no DAT-positive infants among those who received phototherapy. (The number of infants with a positive DAT was small, however). In addition, many infants with a positive DAT had an early and rapidly rising TSB level, prompting treatment with phototherapy earlier in their hospital course. Consequently, many of these infants may not have reached the specific TSB level needed to qualify for the present study.

We found that inpatient phototherapy appears to be at least 85% effective in preventing infants with a TSB from 17 to 22.9 mg/dL from reaching a TSB $\geq$ 25 mg/dL. The effectiveness was not affected by adjustment for co-interventions and additional risk factors and is if anything an underestimate, because any phototherapy started more than 8 hours after the qualifying TSB level was not considered. This finding is similar to the effect reported by Martinez et al¹⁴ when phototherapy was combined with interrupting breast-feeding, but exceeds the 30% to 60% relative risk reductions reported in that and other studies when there was no accompanying change in feeding.^{13,22} Compared with previous studies, our higher efficacy for phototherapy may be related to more intensive phototherapy, higher concentrations of bilirubin in the skin, and a higher endpoint (TSB $\geq$ 25 mg/dL vs $\geq$ 20 mg/dL).

The clinicians in the present study may have preferentially treated infants with phototherapy who were at greater risk of developing high TSB levels. This would have led to confounding by indication, which would tend to diminish the apparent efficacy of phototherapy. However, the strong evidence of a benefit of phototherapy demonstrated in our multivariate analyses suggests that most confounding was controlled for by our matching scheme or that phototherapy was even more efficacious.

Home phototherapy was not associated with the outcome, but only 11 out of 310 infants received it. More data are needed to evaluate the efficacy of home phototherapy for TSB

levels in this range. IVIG may be a helpful adjunct therapy in infants with a positive DAT. Only 5 infants in the study received IVIG, and none of them developed severe hyperbilirubinemia. As previous studies have shown, hydrating infants with intravenous fluids also may help prevent severe hyperbilirubinemia.^{23,24} In our study, 22 infants received intravenous fluids after their qualifying TSB, and none went on to develop a TSB $\geq$ 25 mg/dL. Fourteen of these 22 infants also received inpatient phototherapy. Placing the infant in sunlight had no apparent efficacy.

Our study has some limitations. The study involved a chart review for some variables, and thus some infants may have been misclassified due to incomplete charting. The study was done in a managed-care organization, in which other factors can influence readmission and treatment decisions, possibly limiting the study's generalizability to other populations. We also acknowledge that our outcome (TSB $\geq$ 25 mg/dL) is not a disease and seldom results in adverse effects.¹⁵ Infants are treated with phototherapy to prevent bilirubin encephalopathy; however, given the low incidence of bilirubin encephalopathy, we believe that our outcome of a TSB level at which many physicians would consider an exchange transfusion is reasonable.

In conclusion, when determining the optimal treatment approach for infants with a TSB that has already reached 17 to 22.9 mg/dL at 48 hours or longer after birth, we found that the most important predictors of developing a TSB $\geq$ 25 mg/dL were gestational age, bruising on examination, family history, exclusive breast-feeding after reaching this TSB level, and a rapid rise in TSB. Inpatient phototherapy is very effective in preventing these infants from developing severe hyperbilirubinemia. Such factors as race, sex, and a positive DAT may not be helpful in differentiating which infants will go on to develop severe hyperbilirubinemia. Although excessive weight loss from birth and breast-feeding problems were not predictive in this study, this may be because they led to interventions to improve breast-feeding or provide formula. Although breast-feeding is the optimal approach to infant feeding, supplementation with formula may help reduce the risk of severe hyperbilirubinemia and may be considered in infants close to the TSB threshold for phototherapy.

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Glossary

AAP	American Academy of Pediatrics
AOR	Adjusted odds ratio

DAT	Direct antiglobulin test
IVIG	Intravenous immunoglobulin
KPMCP	Kaiser Permanente Medical Care Program
OR	Odds ratio
TSB	Total serum bilirubin

Figure.
Northern California KPMCP cohort and selection of cases and controls.

Table I
Characteristics of the cases and controls

	Cases (n = 62)	Controls (n = 248)	P value
Variable			
Male, n (%)	38 (61%)	146 (59%)	.7
Birth weight, g	3414 ± 576	3374 ± 527	.6
Gestational age, weeks	37.9 ± 1.4	38.3 ± 1.7	.003
Duration of birth hospitalization, days	2.3 ± 2.3	2.8 ± 2.3	.1
Age at study entry, hours	73.1 ± 17.5	71.5 ± 19.4	.5
TSB at study entry, mg/dL	20.2 ± 1.6	20.1 ± 1.6	.7
Percentage of weight loss from birth *	-6.3 ± 3.7	-6.0 ± 3.5	.4
Matching variables			
AAP risk group			
Low	36 (58%)	144 (58%)	1.0
Medium	24 (39%)	96 (39%)	1.0
High	2 (3%)	8 (3%)	1.0
Difference from AAP phototherapy threshold at study entry, mg/dL	3.6 ± 2.0	3.6 ± 2.0	.9

Values are reported as mean ± standard deviation unless noted otherwise.

* Weight loss from birth to time of study entry (available for 213 patients).

Table II
Bivariate analysis of risk factors for severe hyperbilirubinemia

Variable	Cases (n = 62)	Controls (n = 248)	OR (95% CI)	P value
Demographic				
Male	38 (61%)	146 (59%)	1.10 (0.62 to 1.98)	.7
Asian	17 (27%)	74 (30%)	0.90 (0.49 to 1.63)	.7
African American	5 (8%)	17 (7%)	1.19 (0.43 to 3.30)	.7
Gestational age				
40 + weeks	8 (13%)	73 (29%)	Reference	
38 to 39 weeks	31 (50%)	91 (37%)	2.99 (1.30 to 6.86)	.01
34 to 37 weeks	23 (37%)	84 (34%)	4.36 (0.93 to 20.5)	.06
Birth hospitalization < 48 hours	43 (69%)	141 (47%)	1.75 (0.96 to 3.20)	.07
Age at study entry				
48 to 71.9 hours	37 (60%)	139 (56%)	Reference	
72 to 95.9 hours	15 (24%)	87 (35%)	0.65 (0.31 to 1.33)	.2
≥ 96 hours	10 (16%)	22 (9%)	2.07 (0.73 to 5.92)	.2
History and physical examination				
Feeding before qualifying TSB [*]				
Maternal breast milk	47 (77%)	166 (69%)	Reference	
Formula	1 (2%)	15 (6%)	0.25 (0.03 to 1.90)	.2
Both	13 (21%)	61 (25%)	0.84 (0.43 to 1.68)	.4
Family history of jaundice	5 (8%)	14 (5.7%)	1.48 (0.50 to 4.34)	.5
Breast-feeding problems	12 (19%)	48 (19%)	1.00 (0.50 to 2.01)	1.0
Cephalohematoma on examination	11 (18%)	36 (15%)	1.25 (0.61 to 2.60)	.5
Bruising on examination	26 (42%)	61 (25%)	2.24 (1.24 to 4.04)	.007
Weight loss since birth ≥ 10% [†]	5 (10%)	19 (12%)	1.24 (0.40 to 3.90)	.7
Laboratory values				
Qualifying TSB occurring during birth hospitalization	12 (19%)	80 (32%)	0.48 (0.24 to 0.97)	.04
TSB increase ≥ 6 mg/dL/day	40 (65%)	112 (45%)	2.94 (1.46 to 5.92)	.002
DAT positive	5 (8%)	30 (12%)	0.43 (0.11 to 1.70)	.2
Interventions				
Inpatient phototherapy [‡]	6 (10%)	101 (41%)	0.14 (0.06 to 0.35)	< .001
Home phototherapy [‡]	4 (6%)	7 (3%)	2.57 (0.67 to 9.83)	.2
Exchange transfusion	0 (0%)	2 (1%)	0.00 (0.00 to 6.45)	.3
IVIG	0 (0%)	5 (2%)	0.00 (0.00 to 1.82)	.1
Intravenous fluids after qualifying TSB	0 (0%)	22 (9%)	0.00 (0.00 to 0.36)	.002
Exclusive breast-feeding after qualifying TSB	31 (50%)	76 (31%)	2.29 (1.29 to 4.06)	.005
Physician-recommended sunlight	11 (18%)	35 (14%)	1.30 (0.63 to 2.72)	.5

* Information available for 303 patients.

[†] Weight loss from birth to study entry (available for 213 patients).

[‡] Inpatient phototherapy within 8 hours of qualifying TSB; home phototherapy within 1 day of qualifying TSB.

Table III
Predictors of a TSB $\geq$ 25 mg/dL: Multivariate model

Variable	Adjusted OR (95% CI)	P value
Gestational age		
40 + weeks	Reference	NA
38 to 39 weeks	3.12 (1.21 to 8.03)	.02
34 to 37 weeks	3.74 (0.62 to 22.7)	.15
Family history of jaundice	3.83 (0.93 to 15.7)	.06
Bruising noted on examination	2.36 (1.17 to 4.77)	.02
TSB increase $\geq$ 6 mg/dL/day	2.54 (1.17 to 5.50)	.02
Inpatient phototherapy*	0.15 (0.06 to 0.40)	< .001
Exclusive breast-feeding [†]	2.03 (1.03 to 3.99)	.04

NA, not applicable.

* Inpatient phototherapy within 8 hours of qualifying TSB.

[†] Exclusive breast-feeding after reaching qualifying TSB.